

Deoxyfluorination using CuF₂ enabled by a Lewis base activating group strategy

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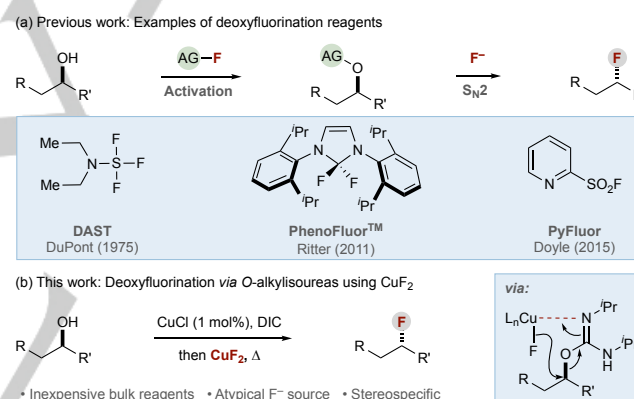
Abstract: Deoxyfluorination is a primary method for the formation of C–F bonds. Bespoke reagents are commonly used due to issues associated with the low reactivity of metal fluorides. Here, we report the development of a simple strategy for deoxyfluorination using first-row transition metal fluorides that overcomes these limitations. Using CuF₂ as an exemplar, activation of an *O*-alkylisourea adduct formed *in situ* allows effective nucleophilic fluoride transfer to a range of primary and secondary alcohols. Spectroscopic investigations have been used to probe the origin of the enhanced reactivity of CuF₂. The utility of the process towards enabling ¹⁸F-radiolabeling is also presented.

The installation of C–F bonds is a fundamental approach towards the modulation of molecular properties within agrochemicals, pharmaceuticals, and materials.^[1] Electronic effects imparted by fluorine have become integral within pharmaceutical and agrochemical development, e.g., enhancing metabolic stability or for radiolabeling applications. In addition, the well-known non-covalent interactions introduced by C–F bonds (e.g., the *gauche* effect),^[2] provides conformational control in a variety of cyclic and acyclic systems and, in turn, exploration of molecular space. Accordingly, methods for C–F bond formation are highly valuable and continue to be advanced.

Deoxyfluorination is one of the most widely used methods for conversion of alkyl alcohols to the corresponding fluorides, achieved by nucleophilic displacement of the activated alcohol by F[−] (Scheme 1a).^[3] This suggests that cheap, readily available metal fluorides (MF_n) would be the ideal reagent for deoxyfluorination. However, the intrinsic properties of MF_n have meant that their direct use in these processes is underdeveloped. These species are generally highly solvated, polymeric, hygroscopic, basic, have high lattice energies, and are often poorly soluble in organic solvents.^[1d,3b,4] To circumvent these issues, bespoke reagents have been developed for deoxyfluorination,^[3,5] including diethylaminosulfur trifluoride (DAST),^[5c] PhenoFluorTM,^[5i] and PyFluor^[5j] (Scheme 1a). These

reagents offer the combined advantages of *in situ* activation of the alcohol, while simultaneously addressing the solubility and reactivity problems of fluoride.

Overcoming the problems with the use of MF_n salts remains a major challenge in this field. There are limited examples of the use of alkali metal fluorides for deoxyfluorination.^[6] Recent seminal studies by Gouverneur demonstrated that KF and CsF can also be used within asymmetric processes.^[7] With regards transition metal (TM) fluorides, AgF and AgF₂ are frequently used as fluoride sources;^[8] however, there are limited examples of other TM salts in fluorination processes,^[9,10] where they are more commonly employed as bases.^[11] Here we show the development of a simple method for deoxyfluorination with typically unreactive TM fluorides, using CuF₂ as an example (Scheme 1b).



Scheme 1. (a) Deoxyfluorination using bespoke reagents. (b) This work. Deoxyfluorination using CuF₂. AG, activating group; DIC, *N,N'*-diisopropylcarbodiimide.

Our approach was based on the proposal that a group used for activation of an alcohol could act as a coordinating group for MF_n. Variation of the activating group would provide a Lewis basic site that could, in principle, be tuned for coordination to a specific metal. This approach may assist in overcoming solubility and hydration issues by providing a vector for chelate-directed F[−] transfer, potentially offsetting the issues with F[−] reactivity when used in an intermolecular process.

An initial screen of TM fluorides and alcohol activating groups revealed CuF₂ and DIC-derived *O*-alkylisourea as a promising system for the deoxyfluorination of benchmark substrate **1a** (Table 1; see ESI for full details). Optimization delivered a system where Cu(I)-catalyzed formation of *O*-alkylisourea^[12] followed by deoxyfluorination using CuF₂ at 100 °C gave **2a** in 78% isolated yield with clean S_N2 (entry 1).

Several optimization points are worth noting: (1) The reaction required formation of the *O*-alkylisourea prior to addition of CuF₂. Reduced efficiency was observed in experiments where all

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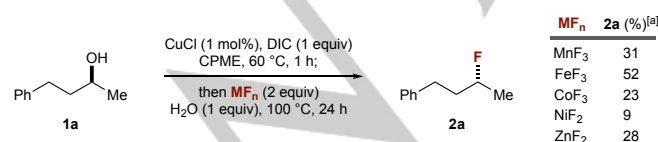
reagents were combined from the outset (entry 2). (2) The addition of H₂O to anhydrous CuF₂ was essential. Removal of H₂O or use of the dihydrate was less effective (entries 4 and 5; *vide infra*). (3) Alternative activating groups were less effective (entries 6–10). (4) The urea byproduct was found to inhibit the reaction, suggesting an absence of advantageous urea•F[−] H-bonding,^[13] and due to formation of Cu(II)•urea complexes (entry 10);^[14] (5) It was possible to use an exogenous fluoride (KF) with stoichiometric Cu(OTf)₂ (entry 11), providing utility within Positron Emission Tomography (PET) radiolabeling (*vide infra*). This process does not operate without Cu(OTf)₂; however, attempts to use catalytic Cu(OTf)₂ were unsuccessful, possibly due to Cu(II) inhibition as noted above.

Table 1. Reaction development.

$\text{Ph-CH(OH)-Me} \xrightarrow[\text{'optimized conditions'}]{\text{CuCl (1 mol\%), DIC (1 equiv), CPME, 60 }^{\circ}\text{C, 1 h; then CuF}_2 \text{ (2 equiv), H}_2\text{O (1 equiv), 100 }^{\circ}\text{C, 24 h}}$ Ph-CH(F)-Me		
Entry	Deviation from 'optimized' conditions	Yield ^[a]
1	None	78 ^[b] (94% es) ^[c]
2	All reagents present from start	21 (19) ^[d]
3	Second stage temperature = 80 °C	34
4	No water	22
5	CuF ₂ •2H ₂ O	27
6	Activating group = acetate	0
7	Activating group = tosylate	16
8	Activating group = methyl xanthate	0
9	Activating group = trichloroacetimidate	32
10	N,N'-diisopropylurea (1 equiv) additive	38
11	Cu(OTf) ₂ (1 equiv), KF (2 equiv), 18-crown-6 (2 equiv), 110 °C, 1 h	57

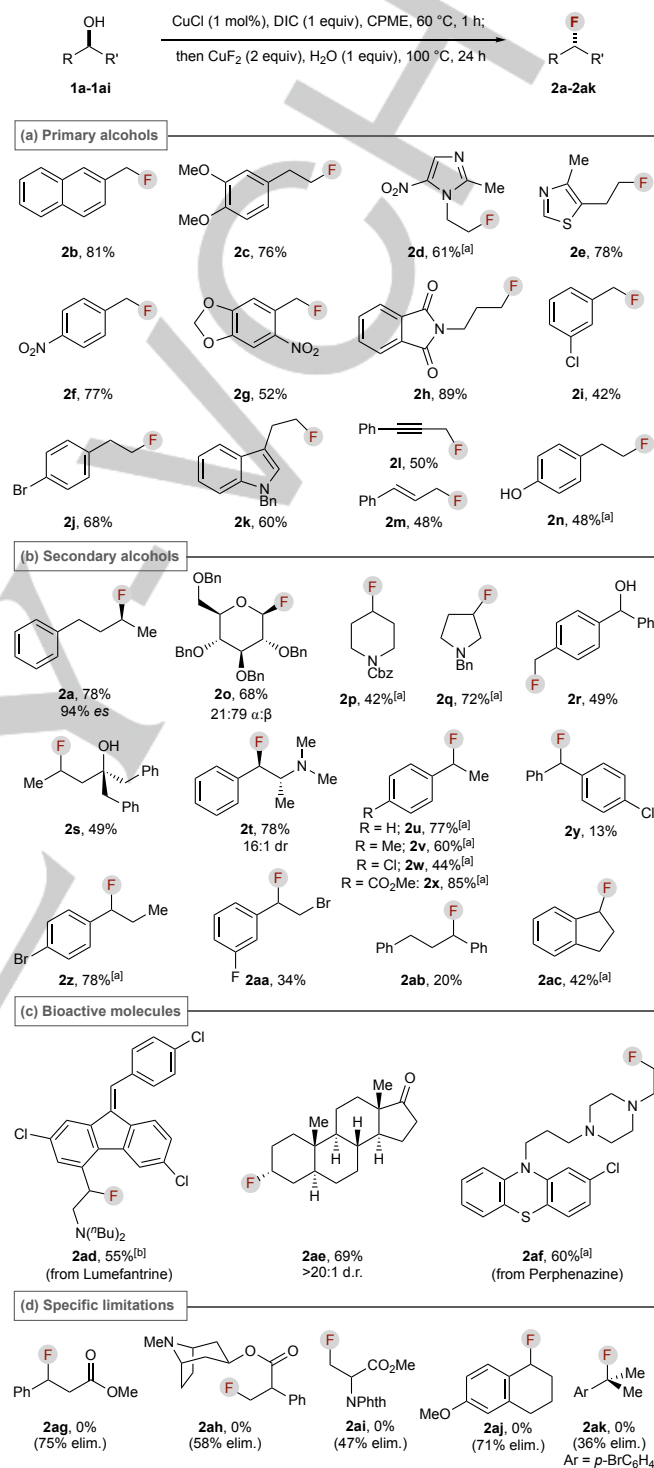
Reactions performed on 1 mmol scale. [a] Determined by ¹H NMR using an internal standard. [b] Isolated yield. [c] Determined by HPLC using a chiral stationary phase. [d] 100 °C from start. CPME, cyclopentyl methyl ether.

Finally, while CuF₂ was selected as an exemplar system, the same process allows deoxyfluorination using a range of other first row TM fluorides (e.g., Scheme 2).



Scheme 2. Use of other MF_n. Reactions performed on 1 mmol scale. [a] Determined by ¹H NMR using an internal standard.

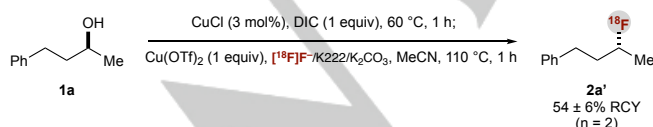
The generality of the CuF₂ process was assessed using a range of alcohol substrates (Scheme 3).



Scheme 3. Example scope. Isolated yields unless noted. [a] Determined by NMR using an internal standard. [b] Reaction performed in 1,4-dioxane.

Primary alcohols were broadly accommodated in good yield (Scheme 3a). A variety of common functional groups were tolerated including aryl halides, heterocycles, and amine protecting groups. The reaction was selective for S_N2 vs. potential S_N2' in systems where this is possible (**2l**, **2m**). Similarly, the reaction was effective for secondary alcohols (Scheme 3b). In addition, the reaction demonstrated high stereospecificity across several substrate types, including simple alcohols (**2a**, 94% *es*) and aminoalcohols (**2t**, 16:1 *dr*), with good diastereoselection also displayed for exemplar sugar substrate **2o** (21:79 α : β). In addition, the reaction was selective for displacement of the *O*-alkylisourea vs. alkyl bromides (**2aa**), consistent with the experimental design. Substrates inclined to S_N1 pathways delivered product but in low yield (**2y**). Specific substrates were noted to undergo efficient fluorination (as determined by ^{19}F NMR of the crude reaction) but were prone to elimination on silica, leading to low yield (e.g., **2ab**, **2ac**). The reaction was chemoselective for primary alcohols in the presence of phenols (**2n**) and secondary alcohols (**2r**), and selective for secondary alcohols over tertiary (**2s**) except for a specific 1,3-diol where unexpected selectivity was observed (see ESI). More complex substrates also delivered the expected products in good yield (Scheme 3c). Finally, specific limitations (Scheme 3d) were observed with substrates liable to elimination (**2ag-2ak**). Experiments to probe whether the approach would operate for other common deoxyfluorination substrates (epoxides, ketones) were unsuccessful, consistent with the activation strategy.

As noted in Table 1 (entry 11), the deoxyfluorination can be achieved using $\text{Cu}(\text{OTf})_2 + \text{KF}$. Based on this, it was envisioned that this method could be readily adapted for radiofluorination.^[15] Radiochemical protocols often differ substantially from the corresponding non-radioactive counterpart, mainly due to the requirement of ^{18}F fluoride as the limiting reagent. However, a proof of concept study with benchmark substrate **1a** showed that this process could be easily adapted for ^{18}F radiolabeling (Scheme 4). From initial radiochemistry experiments, only increased CuCl catalyst loading (from 1 to 3 mol%) was required for optimization of the radiochemical yield (RCY).^[16] Use of the standard reaction conditions from the ^{19}F -protocol and ^{18}F - $\text{F}/\text{K}222$ gave ^{18}F -labeled product **2a'** in $54 \pm 6\%$ RCY ($n = 2$). While radiofluorination can be performed with sulfonate activated secondary alcohols, these are often accompanied with elimination by-products.^[15b,17] Using the controlled reactivity of the directed copper-mediated ^{18}F fluoride displacement of the *O*-alkylisourea adduct in this method allows clean formation of the radiofluorinated product, directly from the alcohol substrate.



Scheme 4. Installation of ^{18}F .

Efforts to understand the operation of the process were difficult based on the heterogeneity of the system and the stoichiometry of $\text{Cu}(\text{II})$, precluding *in situ* monitoring or meaningful

NMR investigations. However, engagement of the *O*-alkylisourea intermediate by $\text{Cu}(\text{II})$ was demonstrated by EPR (see ESI).

In terms of the engagement/activation of CuF_2 , we were intrigued by the results which showed a critical dependence on H_2O : addition of 1 equiv H_2O to anhydrous CuF_2 was essential, with both an anhydrous reaction and use of the dihydrate significantly less effective (Table 1: entry 1 vs. entries 4 and 5). It should be noted that commercial “anhydrous” CuF_2 can contain variable quantities of the dihydrate, which can affect reaction efficiency. Accordingly, we sought to interrogate the nature of the copper species generated using a combination of EPR, solid-state NMR, and powder XRD. It was not possible to directly study anhydrous $\text{CuF}_2 + \text{H}_2\text{O}$ due to heterogeneity within the sample; however, “aged” anhydrous CuF_2 (stored on benchtop under air) offered similar performance to anhydrous $\text{CuF}_2 + 1$ equiv H_2O . We therefore used the aged sample for analysis. EPR proved uninformative due to a lack of resolution of the hyperfine coupling (see ESI). While greater insight was obtained through ssNMR and powder XRD (see ESI), these only demonstrated that the aged sample is essentially a superposition of the two pure phases, suggesting either a unique phase somewhere between anhydrous and dihydrate or mixture of phases.

As a control, it is known that heating $\text{CuF}_2 \cdot 2\text{H}_2\text{O}$ to the threshold temperature of 132°C will produce a $\text{Cu}(\text{OH})\text{F} \cdot \text{CuF}_2$ species with the release of HF and H_2O (eqn 1).^[18]



It is therefore plausible that HF could be produced in small quantities in the present system, which posed the question whether the observed reactivity was due to formation of HF *in situ*. A series of control reactions were therefore conducted to explore the possibility of CuF_2 acting as a masked HF source including treatment of the *O*-alkylisourea with HF and the use of acid- or fluoride-sensitive additives to probe for the generation of HF *in situ* (see ESI). Ultimately, while the generation of HF cannot be ruled out conclusively, the totality of the current data suggests that, if present, this contribution appears to be minimal.

In summary, a simple method for deoxyfluorination using first-row transition metal fluorides has been developed and exemplified using CuF_2 . The process is based on a proposed chelate-driven fluoride transfer that effectively overcomes the reactivity issues associated with these fluoride sources. Control experiments and spectroscopic data suggest $\text{Cu}(\text{II})$ activation of an *O*-alkylisourea with fluoride transfer from a hydrated $\text{Cu}(\text{II})\text{F}$ species. The process can also be leveraged to allow effective ^{18}F installation.^[19]

Acknowledgements

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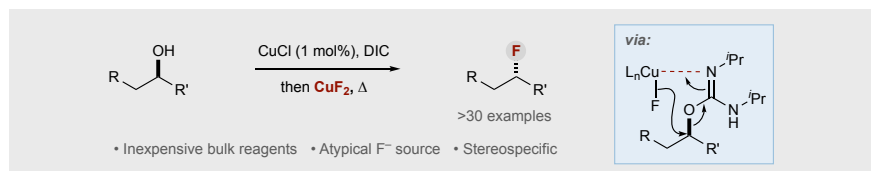
Keywords: copper • deoxyfluorination • fluorine • PET • radiolabeling

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A Lewis base activating group strategy enables deoxyfluorination using first-row transition metal fluorides. Using CuF₂ as an exemplar, activation of an O-alkylisourea adduct formed *in situ* allows effective nucleophilic fluoride transfer to a range of primary and secondary alcohols. Spectroscopic investigations have been used to probe the origin of the enhanced reactivity of CuF₂. The method is also amenable to ¹⁸F-radiolabeling.